UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/704,159	08/28/1996	JAMES A. WILLIAMS	OPHD-02304	8816

7590 07/16/2002

FRANK J. UXA
4 VENTURA
SUITE 300
IRVINE, CA 92618

EXAMINER
LI, BAO Q

ART UNIT	PAPER NUMBER
1648	39

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/704,159	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-112* is/are pending in the application.

4a) Of the above claim(s) *44-46,53, 58-63, 66-78, 81-82, 84-85, 87-88, 95-96, 98-99, 101-102,* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,43,54-57,79,80,83,86,89-91,93,94,100,103-105 and 107-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

Claims 42-112 are pending.

Declaration

The Declaration filed on 05/28/2002 under 37 CFR 1.132 as part of paper No. 38 is acknowledged.

Response to Amendment

This is a response to the amendment, paper No. 36, filed 05/28/02. Claims 54, 66, 93, 97 are amended. New Claims 110-112 are added.

Applicants are reminded to cancel the claims 44-45, 58-63, 81-82, 84-85, 87-88, 95-96, 98-99, 101-102 along with other non-elected claims 46-53 and 66-78 to the non-elected group.

Hence, only claims 42-43, 54-57, 79-80, 83, 86, 89-91, 93-94, 100, 103-105, 107-109 and 110-112 within the scope of the clostridium botulinum toxin A are considered before the examiner.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Double Patenting

Because applicants amend the claims 42, 54-55, 79-80, 93-94 and 107-109 double patenting is moot in view of the new ground of the rejection.

Claim Rejections - 35 USC § 103

Claims 42-43, 54-57, 79-80, 83, 86, 89-91, 93-94, 100, 103-105 and 107-109 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. (Eur. J. Biochem. 1990, Vol. 189, pp. 73-81), Dobeli et al. (US Patent No. 5,310,663) and Ford et al. (Protein Expression and purification 1991, Vol. 2, pp. 95-107) on the same ground as stated in the previous office action.

Applicants argue that there is no motivation for combine the reference because nowhere in the reference for making a recombination to produce the invention as claimed.

Applicants' argument has been respectfully considered. However it is not found persuasive because Thompson et al. teach the entire amino acid sequence of the C botulinum type A neurotoxin (BoNT/A) deduced by nucleotide sequences analysis of the encoding gene (Figure 3). Thompson et al. Teach that the light chain has the pharmaceutical activity (page 73, Column 1). Thompson et al. teach that the increased use of neurotoxins in the food industry, in neurobiological research, and in clinical user, requires immunization of personnel. Thompson et al. also teach that the viability of the BoNT/A gene sequence will allow the production toxin and toxoid for the formulation of improved vaccines (page 83, last paragraph). Thompson et al. in particular, teach the association of receptor binding properties with the C-terminal portion of the heavy chain (page 73). Therefore, there is a strong motivation for the person with ordinary skill in the art to generating a recombinant fusion protein comprising a toxin portion of C botulinum type A toxin in view of the well-known method of constructing a fusion protein in the art as taught by Ford et al and Doideli et al. as described in the previous office action.

Applicants also assert that the cited reference do not provide a reasonable expectation of success for the claimed method. In addition, Applicants filled a Declaration under 37 CFR 1.132 as part of paper No. 38 to argue that the property of "soluble" was not possessed by the prior art and solubility was unexpected result.

Applicant's arguments as well as the Declaration under CFR 1.132, paper NO. 37, filed 05/28/02 have been considered fully, but they are not persuasive to overcome the 103 rejection because the claimed invention is a product, which has same functional structural and function properties as it is disclosed in the prior art. The declaration by Dr. William argues that they used a special promoter to increase the solubility of the recombinant fusion protein of C botulinum type A solubility. This may be a method for making the product, which does not make the claimed product structurally and functionally distinct from the product disclosed in the cited prior art. Therefore, it can not used as the evidence to overcome the obvious type prior art rejection. The rejection maintained.

New Grounds of Rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54, 93 and 110-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant disclosure, the applicants have only disclosed that certain fragments of clostridium botulinum toxin as defined as clones pMA660-110, ppPA 1100-1450, pPA1100-1870, which are able to be expressed as a soluble fusion protein when the particular pET23 vector or pMALc vector are used. No other sequences, which having at lease 4 amino acid residues of any or all clostridium botulinum toxin, is disclosed to be able to expressed as a soluble fusion protein. The specification does not set forth the metes and bounds of that encompasses any or all 4 amino acid residues of any or all clostridium botulinum toxin, there is not enough information about it in literature either to guide the one of ordinary skill in the art to predict the undisclosed any or all random selected 4 amino acid residues from any or all clostridium botulinum toxin, where the region may encompass to the claimed invention. Therefore, a written description of the other claimed sequences encoding at lease from any 4 amino acid residues to the full length of any or all clostridium botulinum toxin should be disclosed to overcome this rejection. See also *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism. 35 USC 112 requires inter alia that "a patent specification contain a written description of the invention and the manner and process of making and using it in such

full clear and concise terms as to enable one skilled in the art to make and use the invention". Case law has made it clear that the requirements for a "written description" and an "enabling disclosure" are separate. For example, where a specification contains sufficient information to enable a skilled chemist to produce a particular compound because it gives detailed information on how to produce analogous compounds but it makes no reference to the compound in question, the "written description" requirement has not been met even though the description may be enabling.

Claim Rejections - 35 USC § 112

Claims 42-43, 54-57, 79-80, 83, 86, 89-91, 93-94, 100, 103-105, 107-109 and 110-112 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having certain fragments of clostridium botuluninum toxin A as defined as clones pMA660-110, ppPA 1100-1450, pPA1100-1870, which are able to be expressed as a soluble fusion protein when the particular pET23 vector or pMALc vector are used, does not reasonably provide enablement for having any or all random selected any figments of the clostridium botulinumn toxin sized from 4 amino acid residues to the full length of any or all clostridium botulinum toxin made as a soluble fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, although it is well know in the state of the art that any protein can be engineered to expressed as a fusion protein. However, it is always unpredictable the solubility of the fusion protein when it is finally expressed. There are multiple factors that influence the solubility of the fusion protein. Sometimes, it is the matter of the protein that you are expressed,

such as size, structure. Sometimes it is the condition of the expression. Sometimes it is the vector that carries the protein. Even in the same condition, Applicants' own disclosure on Table 16 has demonstrated completely different results by using same vector, same condition.

The specification only teach certain fragments of clostridium botulinum toxin A clones pMA660-110, ppPA 1100-1450, pPA1100-1870, which is suitable to be expressed as a soluble fusion protein when they are carried by the pET23 vector and pMALc vector.

The specification is deficient for teaching how to select the fragment ranged from size at least four amino acids to full length minus one of any or all the clostridium botulinum toxin and it does provide any guidance how to select those sequences.

Therefore, considering the scope so broadly read on any or all fragments sized from 4 amino acids to the full length of the amino acids minus 1 of any or all clostridium botulinum toxin, it concluded that undue experimentation would have been required for the person skilled in the art to make and practice the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 42-43, 54-57, 79-80, 83, 86, 89-91, 93-94, 100, 103-105, 107-109 and 110-112 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim1-10 of U.S. Patent No. 5,919,665. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claimed invention is overlapping.

The claims of patent 5,919,665is directed to a soluble recombinant fusion protein comprising the clostridium botulinum toxin A encoded by the SES ID NO" 28, or fragment of clostridium botulinum toxin encoded by the SEQ IS NO: 23 or 26.

Applicants argue that none of the pending claims recites the subject matter identical to the claims of US Patent 5,919,665. In particular, claims 42, 54, 55 and 79 are broadly than the issue claims. Claims 93 and 94 specify " endotoxin free" and claims 107, 108 and 109 specify covalent bonding and therefore, different than the issued claims.

Applicants' argument has been fully considered. However, it is not found persuasive because the claims soluble fusion protein of clostridium botulinum toxin A of the instant Application has 100% identical sequence structure to the soluble fusion protein in the patent 5,919,665 and inherently possess all characteristic of the claimed soluble fusion protein of clostridium botulinum toxin in the patent 5,919,665. Although the instant claims do not cited that the fusion protein contain the poly-histidine tag, the disclose of the specification teaches that the fusion protein is made by fused with the poly-histidine tag. The fusion protein is also claimed as free of the endotoxin. Therefore, the scope of the claimed invention is overlapping with the issued patent No. 5,919,665.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Lapenotiere et al. (Toxicon, 1995, Vol. 33, pp. 1383-1386).

Lapenotiere et al. disclose a method for using the recombinant technique to express a large, nontoxic fragment of botulinum neurotoxin serotype A and the isolated nontoxic fragment of botulinum neurotoxin serotype A (See entire document). Therefore, the claimed invention is anticipated by the cited reference.

Claims 42-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Moberg et al. (Applied and Environmental Microbiology 1978, Vol. 35, pp. 878-880).

Moberg et al. disclosed a method for using the affinity chromatography to purify the type A botulinum neurotoxin and the purified type A botulinum neurotoxin with 99% purity. The isolated toxin is soluble in 0.025 M phosphate buffer, pH 6.3 or 0.1 M NaCl pH 7.9 (see entire document). Therefore, the claimed invention is anticipated by the cited reference.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 05/28/2002 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
July 15, 2002

Baoqun Li

James C. Housel 7/15/02
JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600